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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/306,986	05/07/1999	THUAN QUOC TRINH	0942.4570001	4261

7590 02/11/2003

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/306,986	TRINH ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-13,56 and 70-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13,56 and 70-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/21/2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants amendment of the specification, cancellation of claims 57-69 and amendment of claims 8 and 56 and the addition of claims 70-75, Paper No. 19, is acknowledged. Applicants submission of Formal Drawings, Paper No. 22, 10/21/2002, is acknowledged. Claims 8-13, 56 and 70-75 are at issue and are present for examination.

Applicants' arguments filed on 6/7/2002, paper No. 19, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

Applicants filing of information disclosures, Paper No. 18, filed 6/7/2002, and is acknowledged. Those references considered have been initialed.

Drawings

The drawings submitted have been approved by the draftsperson.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-13, 56 and 70-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 (9-13, 56 and 70-75 dependent form) is indefinite in the recitation of "said template". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8, 9, 10, 13 and 71-73 are rejected under 35 U.S.C. 102(b) as being anticipated by Davey et al. (U.S. Patent No: 5,409,818, issued 4/25/1995).

Davey et al. teach a nucleic acid amplification process which involves the synthesis of RNA and double stranded DNA in a single reaction medium containing reagents comprising multiple DNA polymerases and ribonuclease and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule and sufficient to degrade single-stranded RNA. The double stranded DNA in the above reaction medium, as taught by Davey et al., is both generated during the synthesis process, as well as supplied as the template to be amplified which includes both plasmid cloning

vector DNA and genomic DNA (i.e. calf thymus DNA) (See Example 6). Davey et al. further teach the above process, which includes radioisotope-labeled ribonucleoside and deoxyribonucleoside tri-phosphates in the reaction medium.

Thus claims 8, 9, 10, 13 and 71-73, are anticipated by Davey et al.

Claims 8, 9, 10, 13, and 72 are rejected under 35 U.S.C. 102(e) as being anticipated by Kenten et al. (U.S. Patent No: 6,048,687, filed 6/7/1995).

This rejection was originally stated in the previous office action as it applied to claims 57-59 and 62. In response to this applicants cancelled claims 57-59 and 62.

Kenten et al. teach a method for synthesizing and detecting a specific nucleic acid comprising adding to a sample containing the specific nucleic acid a primer, a DNA-directed DNA polymerase and a ribonuclease along with other components and incubating the reaction mixture for a sufficient time to amplify/synthesize the nucleic acid sequence. The "nucleic acid" referred to by Kenten et al. refers to a polynucleotide of any length, including DNA or RNA chromosomes or fragments thereof (column 7, lines 12-15), and "specific nucleic acid sequence" means a single stranded or double stranded nucleic acid, which clearly includes "double stranded genomic DNA". Thus the preparation taught by Kenten et al. comprises RNA and double-stranded DNA. It is noted that Kenten et al. teach the addition of a ribonuclease, and this is encompassed by claim 9 drawn to a number of specific ribonucleases, as well as fragments, variants derivatives or mutants thereof. Kenten et al. further teach that the nucleotides may be

linked to biotin and digoxigenin, thus encompassing detectably labeled nucleotides as recited in claim 13.

Thus, Kenten et al. anticipates claims 8, 9, 10, 13, and 72.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 70, 74 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davey et al. et al. (U.S. Patent No: 5,409,818, issued 4/25/1995).

As discussed above, Davey et al. teach a nucleic acid amplification process which involves the synthesis of RNA and double stranded DNA in a single reaction medium containing reagents comprising multiple DNA polymerases and ribonuclease and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule and sufficient to degrade single-stranded RNA. The double stranded DNA in the above reaction medium as taught by Davey et al. is both generated during the synthesis process, as well as possibly supplied as the template to be amplified, which includes both plasmid cloning vector DNA and genomic DNA (i.e. calf thymus DNA) (See Example 6). Davey et al. further teach the above process which includes radioisotope labeled ribonucleoside and deoxyribonucleoside tri-phosphates in the

reaction medium. Davey et al. further teach that the "specific nucleic acid sequence" includes any single or double stranded nucleic acid which one wishes to amplify. Davey et al. suggest a possible example of the application of the taught technique include its use as a diagnostic assay for AIDS, based on the presence of an AIDS specific nucleic acid sequence.

One of ordinary skill in the art would have been motivated to use the method of Davey et al. as a means of amplifying any single stranded RNA, single-stranded DNA and double-stranded DNA including those RNAs and DNAs commonly used in general molecular biology techniques. These include vectors such as expression vectors and viral and phage DNAs. Motivation for the use of such methods of synthesizing these nucleic acids include the creation of such vectors for the expression of polypeptides of interest, using standard molecular and microbiological techniques and transforming any known recombinant host cell such as *E. coli, Bacillus* or yeast etc. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Further, as suggested by Davey et al., the use of a specific nucleic acid sequence that is a viral DNA, such as a sequence specific to the AIDS virus would be useful as a diagnostic assay. The reasonable expectation of success comes from the similarity of

the nucleic acid molecules with respect to their enzymatic manipulation, and the results of Davey et al. who successfully used the taught technique to amplify single stranded RNA, single- and double-stranded DNA, and ribosomal RNA templates. Thus Davey et al. makes obvious claims 70, 74 and 75.

Claims 8-12, 70, 71 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Major (Biotechniques, Vol 12, No. 1, 1992, pages 40-43) and Maudru et al. (Journal of Virological Methods 66: 247-261, July 1997).

Major teaches a rapid PCR method of screening for point mutations. The taught method involves ascertaining the presence of a desired mutation within the mutated fragment or within some vector into which the mutated fragment has been cloned. Major teaches a method which comprises the synthesis of a nucleic acid molecule from a preparation comprising RNA and double-stranded DNA, said method comprising mixing the preparation with one or more DNA polymerases and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of a template nucleic acid molecule. The method taught by Major specifically involves the PCR amplification, using *Taq* DNA polymerase, of a DNA fragment from the expression plasmid, pBluescript II SK(+), either sampled directly from JM109 *E. coli* colonies or from a bacterial plasmid isolate. Major further teach that some primers, especially those with a 3'-terminal T:T mismatch result in extra minor bands when bacterial colony lysates were used for the starting material. This thus decreases the

sensitivity of the taught assay. Major does not teach the inclusion of ribonuclease in the taught method of synthesizing nucleic acids.

As discussed in the previous office action, under the 102 rejections, Maudru et al. teach that the background signal of the PCR-based reverse transcriptase assay is due to an intrinsic RNA-dependent DNA polymerase activity of the *Taq* DNA polymerase enzyme and they teach that this background signal could be eliminated by the addition of a ribonuclease to the amplification reaction.

One of ordinary skill in the art at the time of filing would have been motivated to add a polypeptide with ribonuclease activity to the method taught by Major, in order to remove residual RNA sequence contamination from the targeted nucleic acid template in any preparation which would contain substantial amounts of RNA, such as a bacterial colony lysate, in order to decrease the level of background signal from the taught PCR assay. As the ordinary artisan would know that any nucleic acid preparation that has not been purified, such as a bacterial colony lysate, contains substantial amounts of contaminating RNA, the motivation for the removal of these contaminating sequences is that this would increase the sensitivity of the taught PCR assay method from bacterial colony lysates, thus eliminating the need for purification of the template DNA and reducing the time and work needed to perform the assay This is supported by both Major, who teach that some primer sets when used with bacterial colony lysates result in extra minor bands, and Maudru et al. who teach that the background signals of PCR based nucleic acid synthesis reactions is due to an intrinsic RNA-dependent DNA polymerase activity of *Taq* DNA polymerase. The reasonable expectation of success

for the inclusion of ribonuclease in the nucleic acid synthesis reaction of Major comes from the high degree of knowledge in the field of nucleic acid synthesis and the results of Maudru et al. who teach that the simultaneous addition of ribonuclease in order to eliminate background signals in the polymerase chain reaction mix containing *Taq* DNA polymerase did not adversely affect the synthesis of the desired nucleic acid products by PCR.

Thus claims 8-12, 70, 71 and 73 are made obvious by Major and Maudru et al.

Remarks

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
February 6, 2003